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Nononcologic Disease in Patients with Cancer

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Nononcologic medical problems are common in patients with cancer. Failure to evaluate and treat these problems leads to considerable morbidity and mortality in people who often have potential for both comfortable and productive lives. While a physician is sometimes powerless to prevent the progression of underlying cancer, he must not allow a diagnostic category to color his approach. By seeing only an end point which is inevitable for all people, one could be inclined not to treat what is treatable. With clinical judgment, information and the eternal question of diagnosticians, "What else could this be?", a physician can focus not on the inevitability of death but on the quality of life.

"The aim of science is to seek the simplest explanation of complex facts . . . Seek simplicity and distrust it."

ALFRED NORTH WHITEHEAD

". . . the fallacy of attributing to one cause what is due to many causes."

H. S. JENNINGS

"Today is the most important day of your life."

LIKE SYPHILLIS AND SYSTEMIC VASCULITIS, cancer is a great masquerader, often appearing in a cloak of symptoms and signs suggestive of other diseases. Once the presence of malignancy is established, it therefore becomes tempting to attribute all further developments to the cancer. As a consequence, what is thought of on superficial clinical grounds to represent a fatal or untreatable issue of malignancy, may prove at autopsy to be a highly treatable, nononcologic illness. In such a case, timely treatment of the intercurrent problem might have allowed the patient with cancer to return to a functional life for an indefinite period. Conversely, because of many new and effective techniques, cancer may be the only treatable possibility, and its differentiation from untreatable nononcologic disease may be lifesaving. It is the purpose of this article to emphasize the many instances in cases of cancer in which careful evaluation of a patient's problems will significantly improve therapy and prognosis. Particularly in patients in whom malignancy appears to be in control, physicians should always consider other causes for the patients' problems in order to prevent unnecessary morbidity or even mortality which would not be allowed in patients without cancer.

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
ADH = antidiuretic hormone
CSF = cerebrospinal fluid
HCG = human chorionic gonadotrophin
PTH = parathormone
TRH = thyrotrophin releasing hormone
TSH = thyroid stimulating hormone
T_4 = thyroxine

Nononcologic Diseases Mimicking Paraneoplastic Syndromes and Malignant Metabolic Disorders[1,2]

Hypercalcemia

Hypercalcemia is produced by a large variety of benign and malignant processes (Table 1). A history of neoplasm is suggestive. However, even when tissue studies show the presence of cancer, this is not adequate proof that the malignancy is responsible. Biopsy proven cancer may coexist with a benign cause of hypercalcemia; differential points to consider are as follows:

- The ingestion of thiazide diuretics may lead to hypercalcemia and provide a readily correctable cause, although hypercalcemia in this setting may be related to an underlying parathyroid excess.[17]
- The development of hypercalcemia in a patient with hilar adenopathy and erythema nodosum should suggest sarcoidosis.[18] Lymph node biopsy studies may help to clarify the diagnosis; however, nonspecific granulomatous change in lymph nodes may coexist with carcinoma,[19-21] and in dubious cases, mediastinoscopy and biopsy may be necessary.[22]
- Hyperthyroidism can cause hypercalcemia and should be considered in patients with sweating, hyperkinetic states and unexplained tachycardias. Thyroid function studies will lead to the correct diagnosis.[5,6]
- Hypercalcemia may develop in a patient with acute adrenal insufficiency. Such a patient may also have orthostatic hypotension, hypoglycemia and hyponatremia; each of which could represent a cancer-related diagnosis.[23] Despite the frequency of adrenal metastasis in several types of tumor, adrenal insufficiency rarely complicates them.
- Primary hyperparathyroidism may appear in patients with cancer. Farr and co-workers have reviewed the cases of 100 patients with hyperparathyroidism; 34 patients had cancer before, coincident with or after the discovery of a benign parathyroid adenoma.[24] The malignant lesions included those of the breast, stomach, lung, pharynx, kidney and thyroid; each of these tumors is known to cause hypercalcemia independently of primary parathyroid disease. Distinction between neoplasm-induced hypercalcemia and that due to primary hyperparathyroidism can be difficult. A history of renal stones, pruritus, peptic ulcer disease or pancreatitis suggests the long-standing parathyroid adenoma; these findings are generally absent in hypercalcemia resulting from malignancy. Parathormone excess can be determined by radioimmunoassay, and newer immunospecific assays may show ectopic parathormone.[25] Farr's group evaluated hypercalcemia with serial alkaline phosphatase, serum calcium and phosphorus, calcium infusion, tubular phosphate reabsorption and prednisone suppression tests. They considered elevated parathormone (PTH) and elevated calcium to be prima facie evidence of primary hyperparathyroidism. In patients with tumors such as breast cancer, small cell lung cancer[26] and carcinoid[27] which do not produce ectopic PTH, the presence of elevated levels of serum chloride and calcium and a decreased tubular phosphate reab-

TABLE 1.—*Causes of Hypercalcemia*

Benign Causes[9]
Thiazide diuretics
Hyperparathyroidism
Sarcoidosis
Hyperthyroidism[5,6]
Acute adrenal insufficiency
Benign monoclonal gammopathy[7]
Milk alkali syndrome[4]
Acromegaly
Hypothyroidism
Renal insufficiency and transplantation
Diuretic phase of acute renal insufficiency
Hypervitaminosis A[8]
Paget's disease

Malignant Causes[9]

Causes	*Responsible Tumors*
Bone metastasis	Many neoplasms
Ectopic parathormone[10]	Epidermoid carcinoma of the lung
	Renal adenocarcinoma[11]
	Oral cavity cancers
	Bladder carcinoma
	Carcinoma of the penis[12]
	Carcinoma of the breast
	Carcinoma of the parotid[10]
	Reticulum cell sarcoma[10]
Abnormal sterol metabolism	Carcinoma of the breast[13,14]
Prostaglandins[15]	Lung cancer
Unknown	Acute leukemia
	Chronic myelogenous leukemia[16]
Estrogen therapy	Carcinoma of the breast

sorption is strong indication to pursue primary hyperparathyroidism. The serum chloride to phosphate ratio has recently been correlated with hypercalcemia due to excessive PTH production either in patients with primary hyperparathyroidism or those with ectopic hormone production. A ratio greater than 32 strongly suggests a parathormone-related cause and makes consideration of parathyroid adenoma a major one in differential diagnosis.[28] It may be possible to show the location of hyperfunctioning parathyroid tissues by venography and venous sampling preoperatively.[29] However, neck exploration may be an essential part of the diagnostic workup when the primary hyperparathyroidism cannot otherwise be excluded. In more obscure cases in which neck exploration is not revealing, selective venous catheterization for PTH radioimmunoassay or showing the presence of PTH in the tumor may clarify the diagnosis.

Tumors produce hypercalcemia both by distant effects (ectopic hormones, prostaglandin E_2, and abnormal sterols) and by direct bone invasion. At present, only ectopic parathormone is amenable to measurement. It may be assayed in blood and tumor.[25] Serum and urine levels of calcium and phosphate, tubular phosphate reabsorption, and urine cyclic adenosine monophosphate (AMP) and creatinine ratios may give indirect evidence of parathormone effect.

Direct tumor invasion of bone may be assessed by serum alkaline phosphatase, bone scan and bone biopsy; these studies should be obtained in the evaluation of hypercalcemia in patients with cancer. When malignancy is established as the cause, hypercalcemia may be controlled by appropriate antitumor therapy. Hypercalcemia may occur during estrogen therapy of breast cancer with bone metastases. This may be a short-lived side effect in an otherwise good tumor response. The addition of cytotoxic chemotherapy or mithramycin may see the patient through this critical metabolic period to a long remission.[30] Alternatively, estrogen withdrawal and adrenalectomy may be of benefit in such tumors with obvious estrogen responsiveness.

Hypocalcemia

Hypocalcemia is uncommon in patients with cancer, but has been reported in patients with osteoblastic metastases from breast cancer and in one patient with chondrosarcoma.[31-33] In patients who have malabsorption syndromes, short bowel syndrome, severe malnutrition, enteric fistulae, prolonged parenteral alimentation or alcoholism, magnesium deficiency and hypocalcemia may develop.[34-37] Replacement of the magnesium in patients with hypomagnesemia may allow the correction of otherwise refractory hypocalcemia.[38,39]

One of us (B.L.) has followed a patient with extensive abdominal carcinomatosis from primary ovarian cancer. In this patient, long periods of nasogastric tube decompression with parenteral alimentation for incomplete bowel obstructions were required. Muscular cramps, carpopedal spasms and Chvostek sign developed in association with hypocalcemia. Despite parenteral administration of calcium gluconate, the blood calcium level could not be stabilized. A serum magnesium level was obtained and was notably depressed. With magnesium supplementation, the calcium concentration returned to normal and the symptoms resolved.

Hyponatremia

While ectopic antidiuretic hormone production may be a consideration in a large variety of tumors and has been shown to be present in tumor extracts,[40,41] many nononcologic conditions may produce hyponatremia, with and without inappropriate antidiuretic hormone (ADH) secretion[42] (Tables 2 and 3). Workup includes determination of urinary sodium concentration and simultaneous urine and plasma osmolalities. Urinary sodium

TABLE 2.—*Inappropriate Antidiuretic Hormone Syndrome*[43-45,51]

Malignancies—especially with mediastinal involvement
Chemotherapy—cyclophosphamide, vincristine[47,48]
Other drugs—morphine, anesthetics
Tuberculosis[49,50]
Other pulmonary infections
Acute intermittent porphyria[46]
Central nervous system lesions
Myxedema
Respirators

TABLE 3.—*Other Causes of Hyponatremia*

Elevated body sodium
Liver disease
Congestive heart failure
Nephrotic syndrome
Decreased body sodium
Adrenal insufficiency
Renal salt wasting
Hyperosomatic non-ketotic coma
Drugs—diuretics, chlorpropamide, carbamazapine, clofibrate, acetominophen

concentration is dependent on intake in the inappropriate ADH syndrome; decreased in nephrotic syndrome, heart failure and liver disease, and usually increased in adrenal insufficiency, diuretic excess, nonketotic hyperosmotic coma and renal salt wasting.

Inappropriate ADH syndromes are also distinguished from other causes of hyponatremia by a low plasma osmolality with a urine osmolality that is not maximally dilute in the presence of normal renal function.[43-45,51] Azotemia, orthostatic hypotension, elevated serum potassium levels and impairment of cortisol increase following adrenocorticotropic hormone (ACTH) administration are features of adrenal insufficiency but not of the syndrome of inappropriate ADH secretion.

Hypokalemia

When hypokalemia develops in patients with small cell carcinoma of the lung, thymoma, nonbeta islet cell pancreatic tumors, cancers of neuroectodermal origin and many other tumors, one should consider ectopic ACTH production.[52] At the same time, one must consider diuretics, alkalosis, long-standing acidosis, and diarrhea or vomiting as causes. In a malignant ACTH syndrome, hypokalemia exists with cachexia, but often without striae or a cushingoid appearance. In the presence of an elevated plasma cortisol value, Cushing disease is distinguished by dexamethasone suppressibility of ACTH and Cushing syndrome by a low plasma ACTH value.

Hyperkalemia

Tumors may cause hyperkalemia by obstruction of the urinary tract. Hypercalcemia or hyperuricemia due to tumor products or tumor therapy may also lead to renal failure. Hyperkalemia may also occur as a consequence of cyclophosphamide therapy in Burkitt lymphoma.[53] Obstruction of the ureters by neoplasm may be readily amenable to radiation or chemotherapy. Nonmalignant causes of hyperkalemia such as drug induced renal failure, acute acidosis, primary acute and chronic renal diseases, Addison disease and radiation strictures of the ureters should be ruled out. The workup consists of urinalysis and determinations of creatinine clearance in serum and electrolytes in urine. Intravenous or retrograde pyelography is necessary whenever obstruction is considered. Dialysis may be required if conservative measures fail to correct the electrolyte imbalance.

Hyperthyroidism

Symptoms and signs of thyrotoxicosis may be found in patients with embryonal tumors, choriocarcinoma[54] and hydatid moles. Evidence of the tumor is usually obvious. In one case followed by us, the patient had a gestational choriocarcinoma with widespread metastasis to the liver, lungs and brain. The presenting features were high fever, sinus tachycardia and tremors. These symptoms responded to propranolol and methimazole. A serum thyroxine (T_4) level was elevated. The patient expired from the extensive cancer before other studies could be undertaken. The diagnosis can be confirmed by the finding of thyroid stimulating hormone (TSH) or thyrotrophin releasing hormone (TRH) in the tumor tissue.

Distinguishing a functioning metastatic thyroid malignancy from other forms of hyperthyroidism is accomplished by the findings of low plasma TSH and total body I^{131} scan[55] and other evidence of organ metastasis such as on x-ray studies of the chest and bone scans.[56]

Hyperlipidemia

Hyperlipoproteinemias of types I and IV have been found in association with some leukemias and lymphomas; types I, III, and V with dysglobulinemias such as macroglobulinemia, myeloma and lymphoma, and type II with nephrotic syndrome complicating certain neoplasms such as Hodgkin disease. These syndromes are not difficult to distinguish and when tumor-related, respond to successful tumor therapy.

Hypoglycemia

The problem of hypoglycemia may complicate insulinoma, retroperitoneal tumors, and primary or metastatic cancer of the liver.[57] In patients with known cancer, possible benign causes include overdose of insulin or oral hypoglycemic agents; hepatic, pituitary or adrenal insufficiency.

Retroperitoneal tumors are usually obvious causes of hypoglycemia because of their characteristically large mass. We have seen one such patient with extensive retroperitoneal hypernephroma who died as a result of hypoglycemia, refractory to glucagon and even continuous infusion of dextrose. However, the more common retroperitoneal malignancies which cause hypoglycemia are sarcomas (for example, hemangiopericytoma, fibrosarcomas). Surgical procedures that reduce the bulk of these tumors alleviate the hypoglycemia. Finding such tumors at operation is usually

TABLE 4.—*Potential Causes of Gastrointestinal Bleeding in Patients with Cancer*

Malignant erosion into the gastrointestinal tract
Peptic ulcer disease
Gastritis—corticosteroids, aspirin, ethanol, phenylbutazone, reserpine, indomethacin, stress
Esophagitis—reflux, chemical corrosive ingestions (suicide attempt), lower esophageal tears following prolonged emesis
Esophageal varices
Bleeding from colonic diverticulum (may be associated with stricture which resembles carcinoma radiographically)
Colitis—ulcerative, shigella, amoeba
Ischemic bowel disease with infarction
Intussusception and volvulus
Thrombocytopenia or coagulopathy

sufficient proof of the cause of this type of hypoglycemia. Similar considerations apply to primary or metastatic hepatic cancer where nodular hepatomegaly, abnormal results on liver function studies and positive findings on biopsy make the cause of hypoglycemia obvious. Appropriate therapy of the tumor per se is the optimal approach to management of this form of hypoglycemia.

Gynecomastia[58]

Ectopic luteinizing hormone may be produced by a variety of types of cancer of the lung[59] and human chorionic gonadotrophin (HCG) from trophoblastic and nontrophoblastic cancer.[60-62] Of this last group, liver, stomach, pancreas, breast, adrenal and renal malignant lesions, myeloma and melanoma are interesting examples. The benign entities to consider, especially in older men with gynecomastia, include the use of certain drugs (digitalis, reserpine, chlorpromazine, spironolactone, dilantin),[63,64] cirrhosis and hemodialysis.[58,65] In the absence of a suggestive drug history, urine or serum determinations of HCG and other mammatropins can be most revealing.

Medical Diseases Mimicking Organ Involvement by Tumors

Gastrointestinal Tract

Upper Gastrointestinal Bleeding. In advanced carcinoma, including that involving the stomach, bleeding is often not related to the tumor. In 81 patients in whom endoscopy was done for upper gastrointestinal bleeding, Lightdale and coworkers[66] found tumors in 72 percent. Of the patients with tumors, 43 percent had hemorrhagic gastrititis, 22 percent had chronic peptic ulcer and 17 percent had direct tumor bleeding. Of 18 patients with stomach tumors, only in ten was the direct source of the bleeding due to the cancer (Table 4).

The thorough evaluation of patients is mandatory, especially in a patient with cancer whose only life-threatening complication is bleeding. Early endoscopy should be considered strongly, and coeliac angiograms may also be indicated. Management should then bear the same indications as for any other patient. Death by exsanguination is an unacceptable alternative to potential months or years of productive life in a patient with limited, though unresectable cancer.

Intestinal Obstruction. In a review of 117 cases in which intestinal obstruction later developed in patients previously treated for cancer, Ketchum and associates found that in 27 percent it was not related to recurrence of or metastasis from the original tumor.[67] In 9 percent there was a new, and often resectable, primary tumor, and in 18 percent there was no evidence of abdominal carcinoma. In three fourths of the remainder, significant palliation was achieved by operative intervention.

Nonmalignant ileus might result from vascular disorders, electrolyte disturbances, adhesive bands, perforated viscus and pancreatitis. Patients with ileostomies, ileal loops and various conditions associated with prolonged diarrhea or vomiting may become sufficiently hypokalemic for ileus to develop. Appropriate management of nonobstructive ileus can usually be accomplished medically. Obstruction should be managed as for any other patients, with tube decompression for low-grade obstruction and surgical operation for high-grade obstruction. Obstruction due to tumor, such as ovarian carcinoma, may respond to chemotherapy.

Liver Disease. In patients with cancer in whom jaundice or hepatomegaly is present and findings on scan or liver function tests are abnormal, hepatic metastasis is not necessarily present. Various infectious diseases and benign infiltrative conditions may revert either spontaneously or with specific therapy. Hepatic uptake of isotope in the left lobe may be decreased following abdominal radiation therapy for Hodgkin disease. Liver biopsy will often settle the issue. The finding of cancer may offer a better chance of response to therapy and, therefore, may offer a better prognosis than the finding of advanced cirrhosis.

Pancreas. Pancreatitis may be associated with malignancy. Other causes such as drugs (glucocorticoids, isoniazid, thiazides, indomethacin, 6-

mercaptopurine, azathioprine, oral contraceptives, L-asparaginase or salicylates),[68-72] should be considered. However, hypercalcemia, ethanol ingestion and a variety of infections are more likely.[73] Hyperamylasemia with circulating macroamylase has been described in bronchogenic carcinoma[74] and can be documented by finding an elevated serum amylase value with a normal urinary amylase level in the presence of normal renal function. Primary or metastatic cancer of the pancreas can lead to pancreatitis.[75,76] The differential diagnosis is aided by a medication history, serum calcium levels, and the serum-to-urine ratio of amylase, which is low in pancreatitis and elevated in macroamylasemia.

Bones

Positive bone scans can be produced by osteomyelitis, Paget disease, hyperostosis frontalis interna, regional osteoporosis, various arthritides, aseptic bone necrosis, postoperative healing and ankylosing spondylitis.[77] In tumors, the scan may be positive in the absence of radiographic findings.[78,79] In their review of 111 cases, Hopkins and Kristensen[77] showed that the scan may be positive in asymptomatic patients with normal values for alkaline phosphatase. A normal alkaline phosphatase value cannot be relied upon to rule out bone metastasis, and occasionally a negative scan is associated with a positive bone biopsy.[80] In a patient with cancer who has bone pain and in whom there are equivocal findings on bone films, scans and serum alkaline phosphatase studies, bone biopsy is essential. The finding of tumor in such a painful site will lead to the institution of important palliative radiation or chemotherapy and a much more comfortable and functional patient.

Lungs

Several nonmalignant diseases may produce radiologic findings compatible with cancer.[81] These include various infections and pneumoconioses. Interstitial disease may mimic lymphangitic dissemination of tumor. In the face of possible interstitial fibrosis due, for example, to bleomycin, busulfan or nitrofurantoin, or having an unknown cause, a biopsy showing lymphangitic cancer will provide evidence for a potentially treatable cause.

Sarcoidosis,[22] mycobacterial, fungal, and protozoal infections[82] may produce pulmonary infiltrates resembling nodular as well as lymphangitic metastasis.[83] Sickles and associates[84] described three cases in which patients with "obvious pulmonary metastases" had benign intrathoracic processes. When the diagnosis is not certain, the same approach should be used as in patients without evidence of cancer and includes skin tests, sputum cytology and culture, mediastinoscopy and, in many cases, open biopsy. Clues to the nonmalignant nature of the infiltrate may be an atypical presentation; for example, pulmonary lesions without hepatic metastasis in a patient with colon carcinoma or "lymphangitic metastases" noted on x-ray studies in an asymptomatic patient.

Heart

In patients with congestive heart failure and arrhythmias unresponsive to the usual management, as well as evidence of carcinoma of the breast, melanoma, oat-cell carcinoma of the lung or histiocytic lymphoma, the only potentially reversible condition may be the tumor. Establishing directly the presence of myocardial metastasis is exceedingly difficult, other than at autopsy. The absence of other causes such as hypertension and atherosclerosis may be clues. The development of unexplained arrythmia or heart block in a patient known to have potentially cardiotropic tumors such as melanoma and small cell lung cancer is strongly suggestive evidence. When all else fails, and if the particulars of the situation require heroic efforts, a trial of chemotherapy or cardiac irradiation might be given with potentially gratifying results.[85]

Malignant pericardial effusions or constrictive pericarditis such as those due to metastatic breast cancer might well respond to low-dose radiation therapy or chemotherapy. On the other hand, pericarditis itself may be due to previous radiation therapy.[86] If tamponade or constriction is the only life-threatening problem, a pericardial window or decortication should be done.[87] Effusions may also be controlled by local instillation of sclerosing agents.

In a patient with heart failure, one must consider the late effects of adriamycin and daunorubicin therapy as possible causes, particularly with cumulative doses exceeding 550 mg per sq meter. With simultaneous cyclophosphamide or with cardiac irradiation, congestive heart failure may occur at even lower doses.[88] In most patients with anthracycline-induced cardiomyopathy there is a decrease in limb-lead QRS voltage of at least 40 percent compared with a pretreatment tracing.[89] Other causes for congestive heart failure should

TABLE 5.—*Azotemia in Patients with Cancer*

Prerenal
Volume depletion
Addison disease
Congestive heart failure
Severe protein loss—gastrointestinal or renal
Renal vascular occlusion
Hepatic failure
Nephrocalcinosis
Uric acid nephropathy
Drug induced—gentamicin, kanamycin, streptozotocin, phenacetin, high dose methotrexate, etc.
Glomerulonephritis—acute and chronic forms
Nephrotic syndrome—Hodgkin disease, colon carcinoma
Postrenal
Stones—calcium, cystine, uric acid, mixed
Stricture—radiation, tumor
Bladder outlet obstruction—prostatic hypertrophy, neurogenic bladder, foreign body

be considered more likely in the absence of this finding.

The following is an example in point. One of us (B.L.) has seen a patient with thymoma in whom pericardial effusion and life-threatening tamponade developed one year after radiation therapy. The pericardial fluid cytology was interpreted as class V. Biopsies of the pericardium and adjacent ribs showed only inflammatory changes consistent with previous radiation therapy. An assumption of uncontrollable malignancy may well have cost the patient's life.

Kidneys

The nephrotic syndrome has been associated with Hodgkin disease, lung cancer, colon cancer, inferior vena cava obstruction and renal vein thrombosis.[90,91] Radiation nephritis, radiation induced constrictive pericarditis, amyloidosis and of course primary renal disease are other causes for the nephrotic syndrome in patients with cancer. Previous chest irradiation may rarely lead to constrictive pericarditis with nephrotic syndrome. A search for clinical and radiologic evidence for constrictive pericarditis and, where indicated, a renal biopsy should be carried out. Collagen vascular disease complicated by cancer may respond to immunosuppressive therapy. In a patient with a history of abdominal irradiation for cancer, hypertension may develop from radiation nephritis, but appropriate workup should be done to rule out other causes for hypertension. The causes of azotemia are legion, and their investigation should include consideration of the prerenal and postrenal types (Table 5).

Nervous System

In a patient with cancer in whom there is clinical evidence of brain metastasis, the brain scan is the most convenient diagnostic method to uncover the lesions. Equivocal cases may be aided by angiography. More recently, the use of computerized axial tomography, especially when combined with intravenous injection of radiopaque contrast medium, has provided more sensitive and selective evidence of brain metastasis.[92]

In high risk groups of patients—such as those with evidence of cerebrovascular disease, those in whom there is evidence of multiple or surgically inaccessible metastatic lesions, or patients in whom there are very strong clinical grounds on which to suspect metastasis, the use of radiation therapy has a much better risk:benefit ratio than the more aggressive surgical approach. Some patients may present with scan and angiographic evidence of a space-occupying lesion in the central nervous system and no other evidence of cancer by history, by laboratory and radiologic evaluation or by analysis of cerebrospinal fluid. In this group, cytocentrifuge study of the spinal fluid should be done. If results are negative, craniotomy must then be considered.

Elevations of intracranial pressure with papilledema secondary to benign conditions may manifest very much like metastatic or primary brain tumors with headaches which are worse in the morning, aggravated by coughing or straining, blurred vision, and sixth nerve palsy. Acute adrenal insufficiency, hypoparathyroidism, hypervitaminosis A, sinus thrombosis, otitic hydrocephalus, and carbon dioxide retention should be considered in the differential diagnosis.

While brain scan and computerized axial tomography are sensitive indicators of the presence of mass lesions, there is a large variety of distant effects on the nervous system by tumors[93,94] (Table 6). As there are no available tests by which these effects can be ruled in, it is the obligation of the physician to rule out the other treatable causes.

Muscles

While muscle weakness and wasting may represent the myasthenic syndrome described by Eaton Lambert, dermatomyositis[97] or the cachexia-anorexia syndrome, one must exclude problems related to electrolyte imbalance. One of our recent patients who had received radiation therapy for thyroid cancer experienced severe weight loss and

weakness which turned out to be due to excess intake of dessicated thyroid. The symptoms subsided when the dosage was reduced. True myasthenia gravis may be present and is distinguished from the Eaton Lambert syndrome by its involvement of the facial musculature, the decrease rather than increase in strength with repeated contractions and its response to edrophonium chloride solution (Tensilon®) rather than guanidine. Muscle weakness may be associated with thymoma or pancreatic carcinoma.

Systemic Problems Mimicking Cancer

Fever

Fever may be found in patients with retroperitoneal tumors, hepatocellular carcinoma, cancer metastatic to the liver, renal carcinoma, Ewing sarcoma and malignant lymphomas.[98] Even in these circumstances, infection remains the most important consideration.[99,100] In patients with solid tumors involving the abdomen, fevers occasionally result from intra-abdominal abcesses. Evaluation with plain abdominal films, B-mode ultrasound scans, liver-lung scans, and gallium scans may show the site of infection for surgical drainage. Patients with extrahepatic obstructive jaundice due to cancer are prone to ascending cholangitis or portal thrombophlebitis. Here, surgical relief of the obstruction can be lifesaving. In the compromised host, one should proceed with empirical antimicrobial therapy immediately after obtaining routine cultures, even in the absence of a demonstrable cause of fever.[100,101] In leukopenic patients, one must pay particular attention to the possibility of perirectal and pelvic abscesses requiring drainage.

In patients with pneumonitis and no clearly demonstrable pathogen after transtracheal aspiration, lung biopsy must be strongly considered. The risk of death from pneumonia caused by Pneumocystis carinii, Candida albicans, aspergillus, Nocardia or Mycobacteria tuberculosis often exceeds that of this surgical procedure, even in patients with compromised pulmonary function.[102] Fever due to the pyrogenic tumors may respond to administration of indomethacin[103] and those due to fungal infections to prednisone.

Central nervous system infection with Toxoplasma gondii[104] and Cryptococcus are important

TABLE 6.—*Effects of Cancer on the Nervous System*

Direct	*Tumors*
Focal neurologic deficits	Most types
Spinal cord Limb weakness, especially hands spacticity, increased reflexes in lower extremities	Lung, breast, stomach "reticulum cell sarcoma"
Compressive neuropathies of peripheral nerves	
Indirect	
Sensory neuropathy[95]	
Encephalomyelitis Loss of recent memory, hallucinations, seizures, confabulation. Spinal fluid may be normal (40 percent) or have increased protein and round cells.	Oat cell carcinoma of the lung involving frontal, temporal lobe or limbic system
Dementia Diffusely slow electroencephalogram Loss of recent memory	Lung, ovary
Subacute cerebellar degeneration Dysarthria, ataxia, hypotonia dementia No nystagmus No focal signs	Lung, ovary, Hodgkin disease and breast
Peripheral neuropathy Distal weakness, decreased depth Tendon reflexes May respond to steroids	Lung, myeloma, Hodgkin disease[95]
Motor system syndrome Focal amyotrophy or upper limb weakness and fasciculation with increased lower limb reflexes and Babinski signs	Lung[96]
Subacute necrotic myelopathy Rapidly destructive hemorrhagic disease, death in weeks	
Cerebrovascular accidents Due to hypercoaguable states, thrombocytopenia Hyperviscosity syndromes	Pancreas, prostate, lung
Infections	
Slow virus syndromes Progressive multi-focal Leukoencephalopathy	Lymphomas, leukemia

treatable causes of fever in immunologically compromised patients. Low cell counts, high protein and negative cultures in the cerebrospinal fluid (CSF) suggest toxoplasmosis. Serologic tests may confirm the diagnosis. Patients with cryptococcosis may not have organisms apparent on India ink preparations of the CSF. In such cases, CSF and urine cultures may show the presence of the organism. Testing CSF for the polysaccharide antigen of Cryptococcus may be of help in establishing the diagnosis.

Blood

Anemia of patients with cancer may be of "chronic disease" type or autoimmune in nature; however, iron deficiency from occult gastrointestinal bleeding or secondary to anticoagulation often complicates the course of these patients. Clearly, the other common causes of anemia must be considered: folate deficiency, pernicious anemia, drug-induced hemolysis including hemolysis due to alkylating agents,[105] hemoglobinopathies and malabsorption syndromes. On the other hand, myelophthisic anemia, drug toxicity and hemolysis due to hypersplenism are problems found in cancer patients. Evaluation should include examination of the peripheral smear, stools for occult blood, serum iron and iron binding capacity, bone marrow aspiration and biopsy, and spleen scan. Similar considerations hold for platelets and granulocytes. The problems of marrow invasion, myelotoxicity, and hypersplenism significantly affect therapy: for the first, increasingly aggressive chemotherapy; for the second, withholding chemotherapy; for the third, consideration of splenectomy.

Lymph Nodes

Lymphadenopathy occurs in a large variety of settings and may be confused with cancer. One must consider a toxic effect of drugs such as the hydantoins,[106] various infectious causes, collagen vascular diseases and even heroin addiction[107] in the differential diagnosis. Although lymphomas may be difficult to distinguish histologically from these benign conditions, biopsy results frequently will settle the issue. In patients with asymptomatic bilateral hilar adenopathy and negative findings on physical examination, biopsy confirmation of sarcoidosis may not be necessary in otherwise asymptomatic persons,[18] but in patients with a history of cancer, biopsy may be essential for the proper diagnosis.

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